



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 37/66</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/06856</b> <b>(43) International Publication Date:</b> 15 April 1993 (15.04.93)
<b>(21) International Application Number:</b> PCT/AU92/00541 <b>(22) International Filing Date:</b> 12 October 1992 (12.10.92)  <b>(30) Priority data:</b> PK 8865 11 October 1991 (11.10.91) AU PK 9080 22 October 1991 (22.10.91) AU  <b>(71)(72) Applicants and Inventors:</b> GILLIES, Mark, Cedric [AU/AU]; 18 Waratah Avenue, Randwick, NSW 2031 (AU). MORLET, Nigel [AU/AU]; 2/13 Bell Street, Watsons Bay, NSW 2030 (AU). SAROSSY, Marc, George [AU/AU]; 46 Green Street, Narrabundah, ACT 2604 (AU).  <b>(74) Agent:</b> SPRUSON & FERGUSON; G.P.O. Box 3898, Sydney, NSW 2001 (AU).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> TREATING OPHTHALMIC FIBROSIS USING INTERFERON-ALPHA  <b>(57) Abstract</b> <p>The present invention relates to the use of topical interferon-<math>\alpha</math> for the treatment of various forms of fibrosis in and around the eye arising from various ophthalmic diseases and procedures. Specifically the invention relates to alleviation of corneal scarring after laser photoablative refractive keratectomy (PRK). It also relates to the alleviation of posterior (lens) capsular opacification after extracapsular cataract surgery with lens implant; the alleviation of wound scarring following glaucoma filtration surgery. Interferon-<math>\alpha</math> may also be used to coat the lens implant prior to or during implantation. It may also possibly be injected into the eye during eye surgery for inhibiting posterior capsule opacification after cataract surgery and in addition may be injected into the vitreous body to prevent retinal fibrosis and proliferative vitreo-retinopathy, and injected subconjunctivally to inhibit fibrosis and scarring following glaucoma filtration surgery.</p>		

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## TREATING OPHTHALMIC FIBROSIS USING INTERFERON-ALPHA

### Technical Field

The present invention relates to the use of topical interferon- $\alpha$  for the treatment of various forms of fibrosis in and around the eye arising from various ophthalmic diseases and procedures. Specifically the invention relates to alleviation of corneal scarring after laser photoablative refractive keratectomy (PRK). It also relates to the alleviation of posterior (lens) capsular opacification after extracapsular cataract surgery with lens implant; the alleviation of wound scarring following glaucoma filtration surgery. Interferon- $\alpha$  may also be used to coat the lens implant prior to or during implantation. It may also possibly be injected into the eye during eye surgery for inhibiting posterior capsule opacification after cataract surgery and in addition may be injected into the vitreous body to prevent retinal fibrosis and proliferative vitreo-retinopathy, and injected subconjunctivally to inhibit fibrosis and scarring following glaucoma filtration surgery.

### Background Art

15 In the field of ophthalmic surgery, it is known to use excimer laser photoablative refractive keratectomy to sculpt the cornea of the eye in order to relieve refractive errors (e.g. myopia) and a number of corneal conditions and diseases. Specifically, the 193nm argon fluoride excimer laser is able to discretely remove corneal tissue by photoablation without thermal damage to surrounding tissue.

20 Of major concern is the activation of the stromal keratocytes when a wound is made to the stroma. As is well known, the basic response of wounded tissue is to repair the defect and therefore the ophthalmic surgeon when using this technique is confronted with alteration to the biochemistry, morphologic features and tissue function unpredictability brought about by the wound itself and the healing phenomenon.

25 Therefore, even though excimer laser ablation of corneal tissue appears to be an efficient method of removing tissue with minimal damage to adjacent areas, nevertheless the healing process does not always lead to the preservation of transparent corneal tissue.

Previous methods of overcoming this problem have been: application of topical steroids such as prednisolone, prednisolone acetate, prednisolone sodium phosphate, 30 fluoromethalone, fluoromethalone acetate, hydromesterone, dexamethasone, and dexamethasone alcohol. Other compounds tested have been idoxuridine, collagen cross-linkage inhibitors and mitomycin C.

It is an object of this invention to ameliorate the known disadvantages of present techniques when dealing with the wound repair mechanism following photoablative 35 refractive keratectomy.

Interferons are a heterogeneous group of proteins that can inhibit many aspects of the fibrotic response. Originally identified by their well known ability to interfere with the production of viral RNA and protein, they also exert anticellular activities generally considered to be inhibitory, which maybe due to their ability to inhibit the c-myc proto-

oncogene. Type I interferon (viral interferon, interferon- $\alpha$  and - $\beta$ ) is produced in response to viral infection, and type II (immune interferon, interferon- $\gamma$ ) in response to specific antigens or mitogens. Of the different classes,  $\alpha$ -interferon is secreted by leukocytes,  $\beta$ - by fibroblasts and  $\gamma$ - by stimulated lymphocytes. Interferons, particularly interferon- $\alpha$ , have been successfully used in humans for twenty years for the treatment of systemic malignancy.

Considerable interest has recently been shown in the potential of interferon as a treatment for such fibrotic diseases as systemic sclerosis, pulmonary fibrosis and keloid. Fibroblasts are stimulated to produce interferons by many cytokines that mediate wound healing, such as interleukin-1-(IL-1), platelet derived growth factor (PDGF) and tumour necrosis factor (TNF). Interferons inhibit fibroblast chemotaxis and proliferation as well as collagen production, the latter synergistically with TNF- $\alpha$ . Intraperitoneally implanted foreign bodies in mice suffered less encapsulation in the presence of interferon- $\gamma$ , the capsules having a reduced collagen content. Fibroblast glycosaminoglycan production is inhibited by interferon- $\alpha$ , while collagenase production is increased. This deactivation of activated fibroblasts can persist for a long time after a brief exposure to interferon. Of the different types of interferon, the  $\alpha$ - and  $\beta$ - subclasses exhibit a broader antifibrotic spectrum.

The present inventors have recently demonstrated that interferon- $\alpha$  inhibits foetal calf serum and platelet derived growth factor induced proliferation of human tenon's capsule fibroblasts *in vitro*. They suggest that interferons may prove to be of benefit in the treatment of fibrosis following PRK in particular, and of ocular fibrosis in general.

#### Disclosure of the Invention

According to a first form of this invention, there is provided a method for the treatment of corneal scarring in a patient requiring such treatment, comprising administering to the cornea of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for the treatment of corneal scarring in a patient comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.

According to a second form of this invention, there is provided a method for inhibiting opacification of the posterior capsule after extracapsular cataract surgery, in a patient requiring such treatment, comprising administering to the lens capsule of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for this method comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.

According to a third form of this invention, there is provided a method for inhibiting wound fibrosis and scarring after glaucoma filtration surgery, in a patient requiring such treatment, comprising administering to the subconjunctival space of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for this

method comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.

According to a fourth form of this invention, there is provided a method for inhibiting formation of pre-retinal membranes and proliferative vitreo-retinopathy following retinal detachment surgery and/or vitrectomy, following trauma, and as a result of retinal vascular disease (including diabetes, thalassaemia and retinal vein occlusion) in a patient requiring such treatment, comprising administering to the vitreous body or retina of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for this method comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.

Interferon- $\alpha$  2A, interferon- $\alpha$  2B or interferon- $\alpha$  2C or any other type of interferon- $\alpha$  may be used in this invention.

The invention also provides novel protein formulations in which the carrier or diluent is a bioerodable polymer, e.g. a polymer ester (polyanhydride), which may be a copolymer of sebacic acid and bis paracarboxyphenoxybutane; or a poly(ortho) ester.

The method of this invention inhibits the scarring response following a variety of corneal procedures such as photoablative refractive keratectomy; lamellar keratoplasty; lamellar keratectomy; epikeratoplasty; removal of pterygium and keratomileusis.

Typically, the patient on whom the methods of this invention are used is a human. However, the methods would also be able to be used on other mammals.

The methods of this invention may also inhibit scarring after chemical damage to conjunctiva and cornea and may also prevent scarring in pathological conditions such as ocular pemphigoid and StevensJohnson's syndrome, Simplex & Zoster keratitis. It may also inhibit fibrosis in thyroid eye disease, orbital psuedo-tumour and ocular myositis.

Preparation of topical composition drops are made up from Intron A powder (Schering-Plough) or Roferon-A (Roche) to a solution of  $1 \times 10^6$  IU/mL.

Formulation of Intron A is as follows:

$\alpha$ - 2b interferon solution

Dibasic sodium phosphate, anhydrous, USP

Monosodium phosphate, monohydrate, USP

Glycine, ph. eur.

Human albumin solution, ph. eur.

Water for injection, ph. eur.

Drops base may be hypromellose or polyvinyl alcohol for dilution to  $10^6$  IU/mL.

The composition of the present invention may be administered topically as a solution, ointment, or within a collagen shield or similar dissolving corneal contact protective dressing containing conventional, non-toxic, pharmaceutically acceptable carriers, diluents and/or excipients as desired, or by direct injection.

The dosage range of interferon- $\alpha$  may be between about 50,000 and  $50 \times 10^6$  IU

and may be between about  $1 \times 10^6$  to  $20 \times 10^6$  IU/mL. Preferably the dosage is between about  $1 \times 10^6$  and about  $10 \times 10^6$  IU/mL. The interferon- $\alpha$  may be administered in 50  $\mu$ L drops, four times a day for six weeks; or preferably two times a day for one week. Interferon- $\alpha$  may also be administered two times a day for three days or one drop hourly for three days. This dosage range is applicable to the first, second and third embodiments of the invention.

When applied according to the fourth embodiment the interferon- $\alpha$  is given by intravitreal injection within the range of 50,000 to  $5.0 \times 10^6$  IU/0.1mL.

The compositions of this invention may also contain a slow release polymer.

10 The pharmaceutically acceptable carriers, diluents and/or excipients are those well known in the art of ophthalmic surgery and comprise the following: hydroxyethyl cellulose, hypromellose, polyvinyl alcohol, gelatin, polyquad, dextran, castor oil or other vegetable oil e.g. sesame, inert soft white paraffin, liquid paraffin, anhydrous lanolin, sodium hyaluronate, methyl cellulose, potassium sorbate, polysorbate; or sodium  
15 chloride, sodium phosphate, buffers hydrochloric acid bicarbonate, Na citrate (citric acid) boric acid in purified water. They may also be biodegradable polymer esters (polyanhydrides) e.g. sebacic acid and bis paracarboxyphenoxybutane, which are employed in the novel formulations of the invention.

The compositions may also contain preservatives and antiseptics such as:  
20 thiomersal, phenyl mercuric acetate, benzylalkonium chloride, disodium edetate, sodium metabisulfite, polymercuric nitrate, chlorobutol, hyloxapol, povidone, propyl hydroxy benzoate, methyl hydroxy benzoate.

It is preferable that the composition of this invention be applied to the cornea immediately following photoablative refractive keratectomy. As a drop, ointment or  
25 collagen shield *etc.* Where the interferon is applied as a drop, it is preferably to treat the eye thus, four to eight times a day for up to about 6 weeks.

The corneal response may be modified by the pre-treatment with interferon  $\alpha$  drops before PRK. It may also be modified by pre-treatment with steroid drops.

The interferon- $\alpha$  may be prepared from natural sources or may be prepared by  
30 recombinant DNA techniques. All of these techniques would be well known to one skilled in this art.

#### Best Mode and Other Modes for Carrying Out the Invention

An effective amount of interferon- $\alpha$ -2b to prevent corneal scarring after photoablative refractive keratectomy is administered topically to the cornea which has  
35 been subjected to this procedure.

The present invention will now be described with reference to the following examples which should not be construed as limiting on the scope thereof.

## Example 1

Preparation of interferon  $\alpha$ -2B topical composition

Preparation of topical composition drops are made up from Intron A powder (Schering-Plough) to a solution of  $1 \times 10^6$  IU/mL.

5 Formulation of Intron A is as follows:

$\alpha$ -2b interferon solution

Dibasic sodium phosphate, anhydrous, USP

Monosodium phosphate, monohydrate, USP

Glycine, ph. eur.

10 Human albumin solution, ph. eur.

Water for injection, ph. eur.

The drops base is hypromellose or polyvinyl alcohol for dilution to  $10^6$  IU/mL.

## Example 2

The composition of this invention is applied to the cornea immediately following  
15 photoablative refractive keratectomy, As a drop, ointment or collagen shield *etc.* Where the interferon is applied as a drop, it is preferable to treat the eye thus, four times a day for up to about 6 weeks.

The corneal response may be modified by the pre-treatment with interferon- $\alpha$ -2b drops before PRK. It may also be modified by pre-treatment with steroid drops.

## 20 Industrial Applicability

It should be clear that the method of treatment of this invention will find wide use in the veterinary and medical fields.

The foregoing describes only some embodiments of the present invention and modifications obvious to those skilled in the art can be made thereto without departing  
25 from the scope of the invention.

## References

Gipson IK (1990) Archives of Ophthalmology 108 1539.

Cintron C (1990) Archives of Ophthalmology 108 1540.

Binder PS (1990) Archives of Ophthalmology 108 1541.

**Method of Treatment****Claims**

1. Use of interferon- $\alpha$  for treating corneal scarring, for inhibiting opacification of the posterior capsule after extracapsular cataract surgery, for inhibiting wound fibrosis and scarring after glaucoma filtration surgery, or for inhibiting formation of pre-retinal membranes and proliferative vitreo-retinopathy.
2. Use according to claim 1 wherein the dosage of interferon- $\alpha$  is between about 50,000 and  $50 \times 10^6$  IU/mL.
3. Use according to claim 2 wherein the dosage unit is between about  $1 \times 10^6$  to  $20 \times 10^6$  IU/mL.
4. Use according to claim 3 wherein the dosage range is between about  $1 \times 10^6$  and about  $10 \times 10^6$  IU/mL.
5. Use according to any one of claims 1 to 4 wherein the interferon- $\alpha$  is interferon- $\alpha$ -2A.
6. Use according to any one of claims 1 to 4 wherein interferon- $\alpha$  is interferon- $\alpha$ -2B.
7. Use according to any one of claims 1 to 4 wherein interferon- $\alpha$  is interferon- $\alpha$ -2C.
8. A process for preparing a composition of interferon- $\alpha$  comprising formulating interferon- $\alpha$  together with a pharmaceutically carrier, diluent and/or excipient.
9. The process of claim 8 wherein the carrier, diluent and/or excipient is a bioerodable polymer.
10. A process of claim 9 wherein the bioerodable polymer is a polymer ester (polyanhydride) or a poly(ortho) ester.
11. A process of claim 10 wherein the polyanhydride is a copolymer of sebacic acid and bisparacarboxyphenoxybutane.
12. A method for the treatment of corneal scarring in a patient requiring such treatment, comprising administering to the cornea of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for the treatment of corneal scarring in a patient comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.
13. A method for inhibiting opacification of the posterior capsule after extracapsular cataract surgery, in a patient requiring such treatment, comprising administering to the lens capsule of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for this method comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.
14. A method for inhibiting wound fibrosis and scarring after glaucoma filtration surgery, in a patient requiring such treatment, comprising administering to the



subconjunctival space of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for this method comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.

15. The method according to any one of claims 12 to 14 wherein the dosage of 5 interferon- $\alpha$  range is between about 50,000 and  $50 \times 10^6$  IU/mL.

16. The method according to claim 15 wherein the dosage unit is between about 1  $\times 10^6$  to  $20 \times 10^6$  IU/mL.

17. The method according to claim 16 wherein the dosage range is between about 1  $\times 10^6$  and about  $10 \times 10^6$  IU/mL.

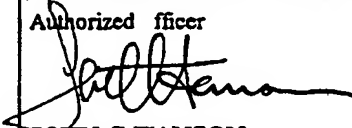
10 18. The method according to any one of claims 14 to 17 wherein the interferon- $\alpha$  may be administered in about 50 $\mu$ L drops four times a day for six weeks.

19. The method according to claim 18 wherein the interferon- $\alpha$  may be administered two times a day for three days.

20. The method according to any one of claims 14 to 17 wherein the interferon- $\alpha$  15 is administered as one drop hourly for three days.

21. A method for inhibiting formation of pre-retinal membranes and proliferative vitreo-retinopathy following retinal detachment surgery and/or vitrectomy, following trauma, and as a result of retinal vascular disease (including diabetes, thalassaemia and retinal vein occlusion) in a patient requiring such treatment, comprising administering to 20 the vitreous body or retina of said patient an effective amount of interferon- $\alpha$  or a pharmaceutical composition for this method comprising interferon- $\alpha$  together with a pharmaceutically acceptable carrier, diluent and/or excipient.

22. The method according to claim 21 wherein the interferon- $\alpha$  is given by intravitreal injection within the range of about 50,000 to  $5.0 \times 10^6$  IU/0.1mL.

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int. Cl. <sup>5</sup> A61K 37/66  According to International Patent Classification (IPC) or to both national classification and IPC					
<b>B. FIELDS SEARCHED</b>  Minimum documentation searched (classification system followed by classification symbols) IPC A61K 37/66 45/02  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC as above					
Electronic data base consulted during the international search (name of data base, and where practicable, search terms used) DERWENT: ALPHA CAS: INTERFERON AND ALPHA AND FIBROSIS OR OPHTHALMIC OR EYE OR OCULAR OR RETINAL					
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>					
<b>Category*</b>	<b>Citation of document, with indication, where appropriate, of the relevant passages</b>	<b>Relevant to Claim No.</b>			
X Y	AU,B, 68201/90 (630530) (BAKER CUMMINS DERMATOLOGICALS, INC) 14 March 1991 (14.03.89). Page 10 lines 23- Page 11 lines 23-28 Page 11 lines 27-28	8 1-4, 12-22			
X Y	AU,B, 68292/87 (601712) (DR KARL THOMAE GESELLSCHAFT MIT BESCHRANKTERHAFTUNG) 6 August 1987 (06.08.87) Page 8 lines 28-37 Page 6 lines 33-36	8, 9 1-4, 12-22			
<div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Further documents are listed in the continuation of Box C.         </div> <div> <input type="checkbox"/> See patent family annex.         </div> </div>					
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> <b>* Special categories of cited documents :</b>   <b>"A"</b> document defining the general state of the art which is not considered to be of particular relevance  <b>"E"</b> earlier document but published on or after the international filing date  <b>"L"</b> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  <b>"O"</b> document referring to an oral disclosure, use, exhibition or other means  <b>"P"</b> document published prior to the international filing date but later than the priority date claimed             </td> <td style="width: 33%; vertical-align: top;"> <b>"T"</b>   <b>"X"</b>   <b>"Y"</b>   <b>"&amp;"</b> </td> <td style="width: 33%; vertical-align: top;">               later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art                document member of the same patent family             </td> </tr> </table>			<b>* Special categories of cited documents :</b>  <b>"A"</b> document defining the general state of the art which is not considered to be of particular relevance <b>"E"</b> earlier document but published on or after the international filing date <b>"L"</b> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) <b>"O"</b> document referring to an oral disclosure, use, exhibition or other means <b>"P"</b> document published prior to the international filing date but later than the priority date claimed	<b>"T"</b>  <b>"X"</b>  <b>"Y"</b>  <b>"&amp;"</b>	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
<b>* Special categories of cited documents :</b>  <b>"A"</b> document defining the general state of the art which is not considered to be of particular relevance <b>"E"</b> earlier document but published on or after the international filing date <b>"L"</b> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) <b>"O"</b> document referring to an oral disclosure, use, exhibition or other means <b>"P"</b> document published prior to the international filing date but later than the priority date claimed	<b>"T"</b>  <b>"X"</b>  <b>"Y"</b>  <b>"&amp;"</b>	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family			
Date of the actual completion of the international search 24 November 1992 (24.11.92)		Date of mailing of the international search report 26 nov 1992 (26.11.92)			
Name and mailing address of the ISA/AU  AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA  Facsimile No. 06 2853929		Authorized officer  JOHN G HANSON  Telephone No. (06) 2832262			

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X Y	AU,B, 77307/87 (590958) (DR KARL THOMAE GESELLSCHAFT MIT BESCHRANKTERHAFTUNG) 25 February 1988 (25.02.88) Page 2 lines 28-33 Page 1A lines 13-18	8 1-4, 12-22
X Y	WO,A, 88/03411 (AMARILLO CELL CULTURE COMPANY, INC) 19 May 1988 (19.05.88) Page 12 lines 4-6 Page 7 lines 13-22	8 1-4, 12-22
X A	EP,A, 82481 (SCHERING CORP) 29 June 1983 (29.06.83) Page 2 lines 7-12	8

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international search report has not established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	630530	DE	3019761	GB	2051521	JP	55161457
AU	601712	DE	3603444	EP	231816		
AU	590958	DE	3628468	EP	258683	US	4824674
WO	88/03411	EP	341258	US	5019382		
EP	82481	DE	3262575	EP	82481		
END OF ANNEX							